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Phosphate and Kidney Healthy Aging

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Abstract: **BACKGROUND** The aging population is increasing rapidly, much faster than our understanding on how to promote healthy aging free of multimorbidities. The aging kidney shows a decline in its function. Whether this decline is preventable or physiological is still debated. Main risks factors for developing CKD are aging common comorbidities, such as hypertension, diabetes, and obesity. Phosphate is vital for our organism, but it is also present in a great variety of food products as food additive and preservative. Due to the higher consumption of processed food in the last century, concern has arisen if a chronic high consumption of phosphate may be toxic impacting on healthy aging. **SUMMARY** Several studies show an association between higher serum phosphate levels and a higher risk of overall mortality and cardiovascular disease. Moreover, higher phosphate levels also worsen CKD progression and may contribute to renal dysfunction in healthy individuals. Acute high phosphate intake is rare but can cause acute kidney injury. Yet, the question if controlling phosphate intake may modulate serum phosphate concentrations remains unanswered, as assessment of phosphate intake is still a difficult task. Phosphate consumption estimations by dietary recalls are largely underestimated, especially in populations groups consuming high amount of processed food. **Key Message:** A healthy diet with phosphate source from food may contribute to promote healthy aging and longevity.

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Review Article

Phosphate and Kidney Healthy Aging

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Keywords

Aging · Phosphate · Chronic kidney disease · Cardiovascular disease · Mortality

Abstract

Background: The aging population is increasing rapidly, much faster than our understanding on how to promote healthy aging free of multimorbidities. The aging kidney shows a decline in its function. Whether this decline is preventable or physiological is still debated. Main risks factors for developing CKD are aging common comorbidities, such as hypertension, diabetes, and obesity. Phosphate is vital for our organism, but it is also present in a great variety of food products as food additive and preservative. Due to the higher consumption of processed food in the last century, concern has arisen if a chronic high consumption of phosphate may be toxic impacting on healthy aging. **Summary:** Several studies show an association between higher serum phosphate levels and a higher risk of overall mortality and cardiovascular disease. Moreover, higher phosphate levels also worsen CKD progression and may contribute to renal dysfunction in healthy individuals. Acute high phosphate intake is rare but can cause acute kidney injury. Yet, the question if controlling phosphate intake may modulate serum phosphate concentrations remains unanswered, as assessment of phosphate intake is still a difficult task. Phosphate consumption estimations by dietary recalls are largely underestimated, especially in populations groups consuming high amount of processed food. **Key Message:** A healthy diet with phosphate source from food may contribute to promote healthy aging and longevity.

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Introduction

Genetically, humans are predetermined to have a maximal life span of 122 years [1]. Whether true or not, currently, the highest regional life expectancy worldwide is on average 84.7 years [2]. In the last century, life expectancy has rapidly increased due to advances in

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health care and public health, but also the incidence of multimorbidities has increased. In 2010, nearly half of the total disease burden in high-income countries was attributable to people aged 60 years and older [3]. Chronic noncommunicable diseases, such as cardiovascular diseases and cancer, cause most of the burden. Therefore, increased life expectancy is not only seen positively, and the terms “grey-tsunami” or “silver-tsunami” compile the fear that an increased aging society may overwhelm the social and health systems [4]. In the last decade, many efforts have been put to understand how to promote healthy aging [5]. The World Health Organization has launched the proposal for a *Decade of healthy aging 2020–2030* in order to promote a concerted, catalytic, sustained collaboration worldwide to confront this challenge [6]. As the process of aging is not yet completely understood, more research is needed before attempting to successfully promote healthy aging.

The seek for an elixir that guarantees eternal youth, also called the philosopher’s stone or liquid gold, started already in times of the great ancient civilizations. This search has preoccupied many alchemists during millennia. The alchemist Henning Brand (around 1630–1710), instead of finding liquid gold, isolated the element phosphorus. Nowadays, high consumption of phosphorus is perceived as a poison instead of an elixir when attempting a prolonged and healthy life [7, 8]. The aim of this review was to analyze published literature on human studies on how phosphate affects healthy aging with special emphasis on kidney health.

Is Kidney Aging a “Treatable” Condition?

Over 300 definitions try to explain what aging means [4]. One view is that biological aging is the process of a change in the organism, which over time decreases the probability of survival and reduces the physiological capacity for self-regulation, self-repair, and adaptation to environmental demands. For humans and many mammals, 9 hallmarks of aging have been proposed including telomere attrition and deregulated nutrient sensing [9]. These processes are irreversible, but amenable to modifications. Chronic diseases are probably the accumulation of insults over years that become apparent with age [4]. Yet, aging is a risk factor for many chronic diseases, but it is not a casual or necessary factor.

Studying healthy kidney donors have suggested that healthy aging causes renal structural changes and a decline in kidney function [10]. At the macroscopic level, there is a decrease in the cortical volume and in the cortical/medullary ratio after 50 years of age [11]. The appearance and size of kidney cysts increases after 60 years of age [12]. Nephrosclerosis increases with aging and the number of nephrons decreases [10], and kidney capacity to acidify urine and excrete an acid load diminishes [13]. Probably, the most controversial point is if the decline in glomerular filtration rate (GFR) observed when aging is physiological or preventable [14]. After 50 years of age, the eGFR declines about 1.15 and 1.45 mL/min per 1.73 m² per year after 70 years of age [15, 16]. This GFR decline is highly variable among individuals [17]. Therefore, some nephrologists claim that the GFR decline with age may be preventable [18], whereas others claim that it is a physiological process, and therefore, the criteria for diagnosis of CKD in aged adults has to be revised [19, 20].

This debate is important because of its medical and social consequences. CKD is currently defined as GFR <60 mL/min per 1.73 m² or the presence of kidney damage markers such as albuminuria for >3 months [21]. Albuminuria is not present in healthy aged adults. Based on this definition, epidemiological studies – mostly measuring eGFR once – have indicated a high prevalence (47%) of CKD among older people aged over 70 years [10]. Therefore, do this people truly suffer from kidney disease? Do they have to be treated as CKD patients with dietary restrictions and medication which could impair their well-being? Or the GFR threshold

should be changed to <45 mL/min per 1.73 m² for adults aged over 65 years to adequately promote healthy aging? [20]. Is perhaps this renal function decline when aging preventable? Hypertension, diabetes, and obesity are the major classical risks for developing CKD [22]. These morbidities are in part preventable by diet, reducing salt, fat, and sugar consumption and energy intake. Low protein diets, which achieve low phosphate intake, are probably the most effective dietary habit to slow disease progression in CKD patients [23]. Therefore, may dietary habits protect kidney function? All these questions remain open but are crucial to promote kidney healthy aging.

Phosphate

Most phosphate (85%) in the organism is found in bone; 14% in soft tissue, viscera, and muscle; and only 1% in the extracellular space. Phosphate has a wide variety of functions: in bone, it forms hydroxyapatite, is part of the backbone of DNA and RNA, is present in phospholipids and in the cellular energy carriers, is essential for pH regulation, and many intracellular signaling processes depend on phosphorous containing molecules [24]. Plasma concentration of phosphate in adults typically range from 0.8 to 1.5 mM and is controlled by a complex endocrine network comprising parathyroid hormone, calcitriol, fibroblast growth factor 23 (FGF23), and α Klotho [25]. The kidney plays the predominant role in controlling plasma phosphate levels. Approximately 80–95% of the filtered phosphate is reabsorbed in the kidney by sodium/phosphate transporters NaPi-IIa and NaPi-IIc, which are regulated by parathyroid hormone and FGF23 [26]. FGF23 also inhibits calcitriol synthesis in an attempt to reduce phosphate absorption in the intestine when phosphate levels in plasma rise [27]. Adults aged 30–90 years have similar phosphate concentrations [28]. Both, hypo- and hyperphosphatemia lead to disease.

Phosphate is widely available with diet, with much higher bioavailability in products derived from animal than vegetable origin [29]. Of concern is the presence of inorganic phosphate in many food products as additives with a very high bioavailability, over 80% [29, 30]. Consuming a high phosphate diet by including processed food increases phosphate consumption by 250–1,000 mg daily as relative to no consumption of processed food [31]. Assessment of dietary phosphate is complicated and mostly underestimated, as the amounts of food additives and preservatives containing phosphate are not reported in food labels. Several studies indicate that the average phosphate intake in the population varies between 800 and 1,600 mg/day, with some individuals reporting very high phosphate intake, around 3,500–5,000 mg/day [28, 32–37]. Over 30 years, an increase in phosphate consumption by 12% was observed [38]. As the US recommended dietary allowance (RDA) of phosphate for adults is around 700 mg/day [39], concern has arisen if a chronic high phosphate consumption may be harmful for health [7, 8]. Moreover, alterations in phosphate homeostasis in mice by ablating FGF23 or α Klotho function leads to premature aging, and this phenotype could be rescued by a low phosphate diet [40]. This review focuses on the evidence on phosphate and its impact on health.

Phosphate and Kidney Health

Rare but recognized are cases of acute kidney injury after administration of high sodium phosphate enemas for bowel cleansing before colonoscopy [41]. Histological analysis revealed the presence of calcium phosphate crystals in the kidney. This condition is called acute phosphate nephropathy and often these patients develop CKD. Early intervention studies in humans

have revealed that large doses of phosphate (>2,250 mg/day on top of dietary phosphate) over 1–7 years increase the appearance of soft tissue calcifications and impair renal function [42].

Adeney et al. [43] analyzed a subgroup with moderate CKD within the US Multi-Ethnic Study of Atherosclerosis (MESA) cohort. This subgroup comprised the older population with an average age of 70 years. The mean eGFR was 50.6 mL/min per 1.73 m² and 97% of the participants had CKD stage 3. Interestingly, using the proposed CKD aged adapted classification [20], most of the participants will be considered kidney healthy aged subjects. Ninety-five percent of the participants had normal serum phosphate levels (mean 1.16 mM). This cross-sectional study revealed that higher phosphate levels – still in the normal range – were associated with decreased kidney function. Also in a cohort with a mean age >65 years and CKD stages from 1 to 5, Schwarz et al. [44]. observed that participants in the 2 highest quartiles – serum phosphate concentration between 1.23 and 1.39 mM and greater than 1.39 mM – had a higher risk to accelerate kidney dysfunction than participants with lower serum phosphate concentrations (<1.07 mM). Therefore, in aged adults, high serum phosphate levels are associated with kidney dysfunction.

Phosphate and Risks Factors of CKD

Diabetes and hypertension are 2 of the main risk factors for CKD [22]. Within the large prospective French E3N cohort, including women born between 1925 and 1950, Mancini et al. [45] observed an average phosphate intake of 1,477 mg/day. Compared with the women with lower phosphate intake (<1,203 mg/day), all 3 other quartiles with higher phosphate intake had a higher incidence of diabetes type 2.

Alonso et al. [32] studied individuals aged 45–84 years from 2 different US cohorts, the Atherosclerosis Risk in Communities Cohort (ARIC) and the MESA cohort, excluding those with hypertension, diabetes, and prevalent cardiovascular disease at baseline. Average phosphate intake was around 1,100 mg/day. High phosphate intake was associated with a lower risk incidence of hypertension, but only when phosphate consumed from dairy products was considered. Therefore, this risk reduction may be due to phosphate in combination with dairy components or to dairy metabolites alone. Of note, calcium present in dairy products may complex intestinal phosphate and thereby even reduces its bioavailability. Mazidi et al. [35]. found also an inverse significant correlation between phosphate consumption and systolic and diastolic pressure. This cross-sectional study was performed in Iran with individuals aged 35–64 years (Mashhad Stroke Heart Atherosclerosis Disorder (MASHAD) study) without a history of a cardiovascular event. Mean phosphate intake was around 1,200 mg/day. Yet, a recent intervention study with 20 healthy young subjects consuming a 17.5 mg/kg body weight on top of the phosphate intake during 11 weeks showed an increment in the pulse rate, systolic, and diastolic blood pressure when compared with subjects consuming a low phosphate diet (normal phosphate diet and consumption of phosphate binders) [46]. Therefore, whereas epidemiological studies indicate a positive action of high phosphate intake in reducing blood pressure, a controlled intervention study ran for 11 weeks in young individuals observed the opposite effect.

Phosphate and Aging

McClelland et al. [47] investigated the association of serum phosphate with biological age with a cross-sectional design. The pSoBid cohort includes UK participants aged between 35 and 64 years. Higher phosphate levels were associated with markers of higher biological age such as

lower telomere length, DNA hypomethylation, and increased inflammatory status. This effect was larger in males with lower economic status and was also associated with increased red meat consumption. Among the most deprived males was also a higher prevalence of early stage CKD.

Phosphate and Risk of Mortality

Chang et al. [28] analyzed a subgroup of healthy participants without known diabetes, cardiovascular or renal disease (aged 20–84 years) within the US NAHNES III Study. Average phosphate intake was 1,166 mg/day. Most subjects consumed between 700 (RDA) and 1,400 mg/day of phosphate and 35% consumed >1,400 mg/day. Phosphate intake higher than 1,400 mg/day was significantly correlated with a higher all-cause mortality. Below 1,400 mg/day of phosphate intake, there was no association between mortality and intake.

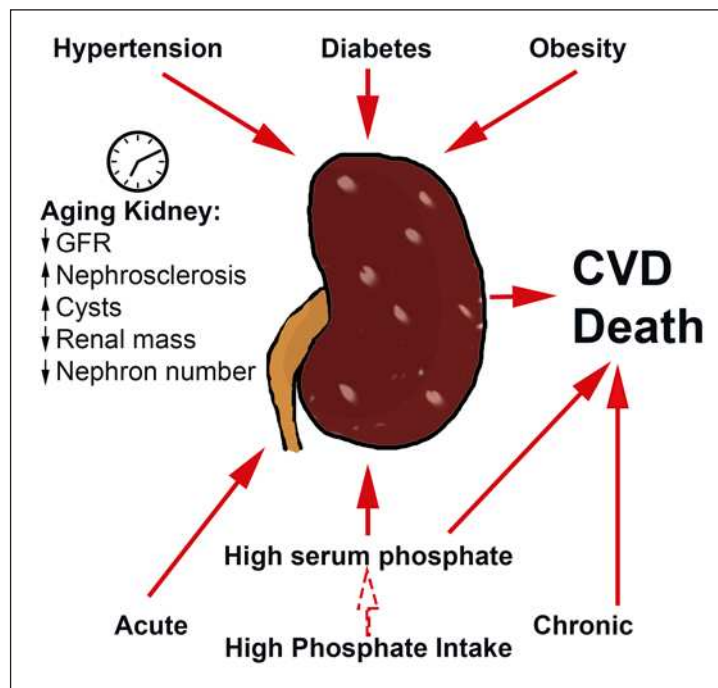
Higher serum phosphate levels have also been associated with a higher risk of overall mortality in patients with CKD and in the general population. Participants of the Chronic Renal Insufficiency Cohort (CRIC) Study with CKD stages 3 and 4 (average age around 65 years) showed a step-wise increased mortality risk with higher serum phosphate concentrations [48]. This association was not found in participants with CKD stage 5. A further study showed also an association between higher serum concentrations (>1.13 mM) and higher mortality risk in patients with CKD. Mortality risk increased linearly with each 0.16 mM increase in serum phosphate levels [49]. Of note, the sample of the study was data from the Veterans' Affairs Consumer Health Information and Performance Sets (CHIPS) Dataset. Mean average age was around 70 years at baseline with overrepresentation of males (around 96%); 67.4% of the participants were classified as CKD stage 3, although only 10% were treated in a nephrology clinic. The Cr clearance values in this population ranged from 35 to 56 mL/min. These data show that mild renal dysfunction in aged adults combined with higher serum phosphate concentrations also associates with a higher mortality risk.

In the general population, Larsson et al. [50] investigated participants (eGFR >60 mL/min per 1.73 m²) from the Uppsala Longitudinal Study of Adult Men Cohort in Sweden for a median follow-up of 30 years. They found that serum phosphate levels above 0.9 mM were associated with higher cardiovascular and all-cause mortality compared to participants with levels below 0.8 mM. This association was also found when investigating only subjects with eGFR >90 mL/min per 1.73 m². This study suggests that mild hypophosphatemia may be beneficial to prolong life. Onufrak et al. [51] found gender differences when investigating participants of the ARIC (aged between 45 and 64 years) with normal renal function. Men with phosphate serum in plasma in the highest quartile (>1.23 mM) had a higher risk of developing cardiovascular disease and overall mortality [51]. This was not observed in the female population, although at baseline, women showed higher serum phosphate levels than men (1.15 vs. 1.05 mM on average).

Phosphate and Cardiovascular Health

Yamamoto et al. [36] found a positive correlation between left ventricular mass (LVM) and phosphate intake. Each quintile increase in the phosphate intake was associated with a 1.1 g increase in the LVM. Two cross-sectional studies found no correlation between phosphate intake and intima-media thickness and coronary artery calcification [33, 34]. Yet, Kwaw et al. found a positive correlation between high phosphates in plasma (>1.25 mM) and the prevalence of coronary artery calcification. Median dietary phosphate in this Korean population was 760 mg/day and median phosphate serum concentrations 1.13 mM.

Fig. 1. Phosphate and kidney aging. Kidney aging implies lower GFR, renal mass and nephron number, and higher appearance of cysts and nephrosclerosis. High serum phosphate levels are associated with renal dysfunction accelerating aging and with cardiovascular disease risk and death. Although the influence of phosphate intake on serum phosphate levels is unclear, chronic high phosphate consumption increases mortality and cardiovascular disease risk. Acute high phosphate intake leads to acute kidney injury and ultimately to CKD. Hypertension, diabetes, and obesity are known risk factors of developing CKD. GFR, glomerular filtration rate.



Further studies have shown an association between high phosphate serum and the development of cardiovascular disease. In the Framingham Offspring Study with 3,368 US participants free of CKD and CVD (mean age 44 years), each 1 mg/dL higher phosphate level in plasma was associated with a 31% increased risk of the first cardiovascular event [52]. In the Cholesterol and Recurrent Event (CARE) study, each 1 mg/dL higher phosphate level in plasma was associated with a 27% greater risk of all-cause mortality in people with prior myocardial infarction [53]. Yet, within the ARIC study, higher serum phosphate was associated with higher risk of death and stroke, but not with coronary heart disease in a population with normal kidney function [54].

CKD patients with higher serum phosphate levels have also a higher incidence of cardiovascular disease. Participants within the Quality Improvement in Chronic Kidney Disease (QICKD) cohort followed up over a period of 2.5 years were separated in 3 groups based on their renal function [55]. Of note, participants in CKD stages 3–5 were significantly older than participants in the other groups (72.8 years vs. approximately 55 years). Higher serum phosphate levels between 1.25 and 1.5 mM were associated with increased cardiovascular risk in participants with normal and CKD stages 1–2, whereas phosphate <0.75 mM was associated with lower cardiovascular risk in subjects with normal renal function. Participants with CKD stages 3–5 and phosphate >1.5 mM had increased cardiovascular disease risk. Unfortunately, this study did not look at the incidence of cardiovascular risk in older subjects classified only as CKD stage 3.

Does Phosphate Intake Determine Serum Phosphate Concentrations?

One study found a correlation between phosphate intake and serum phosphate levels [54], but others found disparities in outcomes or weak correlation [27]. Intriguingly, in several studies, participants reporting higher phosphate consumptions were often younger

and more physically active [28, 45]. Moreover, higher serum phosphate levels in plasma are linearly correlated with lower socioeconomic state in CKD patients and the general population [56, 57]. Yet, the correlation between phosphate intake and socioeconomic status was inverse [57]. As groups with low socioeconomic status tend to eat higher amounts of processed food, these results suggest the well-known underestimation of the dietary record methods for phosphate intake [29, 58, 59]. Epidemiological studies commonly use (single) 24-h dietary recalls or food frequency questionnaires. These methods, although valid, rely on the food databases, where the content in phosphate reported is clearly lower than the real content for most processed food products.

Recently, the European Food and Safety Administration (EFSA) has recommend an acceptable daily intake (ADI) of phosphate of 40 mg/kg body weight per day, which means 2,800 mg/day for a person weighing 70 kg [30]. This value is far beyond the US RDA but suggests that most of the population is consuming an adequate phosphate amount to prevent toxicity. EFSA claims that the human intervention and epidemiological studies do not support enough evidence for assessing an ADI. Therefore, EFSA extrapolates ADI from older animal studies using a no-observable-effect level after a chronic phosphate consumption for 2 years [30]. Yet, the panel recommends the European Commission to set a maximum permitted limit (MPL) for phosphates in food supplements.

Conclusion

As summarized in Figure 1, kidney aging involves lower renal function, reduced renal mass, and lower nephron number, whereas the number and appearance of cysts and nephrosclerosis increase. In aged adults, human studies suggest an association between higher serum phosphate levels – in the normal range – and accelerated kidney dysfunction, higher mortality rate, markers of higher biological age, and higher cardiovascular risk. Less conclusive are studies on phosphate consumption on healthy aging due to the limitations in assessing phosphate intake, as it is present in a great variety of processed food with no obligation to report the content. Yet, despite probable underestimation, prospective studies suggest that higher consumption of phosphate above double the US RDA, are associated with higher mortality rate. More studies with validated markers of phosphate consumption are needed to investigate its impact on health. Despite these limitations, probably a healthy diet with no processed food may promote kidney healthy aging.

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Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

Isabel Rubio-Aliaga wrote all content of the manuscript and therefore is the sole responsible for it.

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